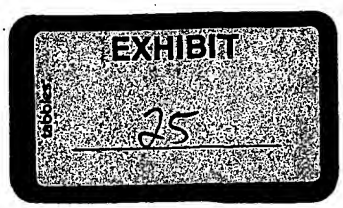

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Caspase-3 and apoptosis in experimental chronic renal scarring.

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BACKGROUND: Caspase-3 is a member of the caspase enzyme family, having a central role in the execution of apoptosis. However, the significance of Caspase-3 in the inappropriate and excessive apoptosis that contributes to the progression of non-immune-mediated renal scarring has not been established. METHODS: Kidneys from sham-operated and subtotal nephrectomized (SNx) rats were harvested on days 7, 15, 30, 60, 90 and 120 post-surgery. These were analyzed for apoptosis (in situ end labeling of DNA, light and electron microscopy), Caspase-3 activity (fluorometric substrate cleavage assay), protein and mRNA (Western and Northern blotting), as well as distribution (immunohistochemistry), inflammation (ED-1 immunohistochemistry) and fibrosis (Masson's Trichrome staining). RESULTS: Apoptosis, inflammation and fibrosis gradually increased in glomeruli, tubules and interstitium of SNx rats. Caspase-3 was mainly located in damaged tubules, but also was found in some glomerular and interstitial cells. Little or no staining was noted in sham-operated kidneys. In SNx kidneys, Caspase-3 activity was significantly increased from day 30 and peaked on day 120 (2.5-fold). This resulted from increases in the 17 and 24 kD active protein subunits. The 32 kD precursor was increased at all time points (1861% on day 120, $P < 0.01$). Caspase-3 changes were transcription-dependent with the 2.7 kb caspase-3 mRNA significantly increased at all time points (287% on day 120). Caspase-3 activity was a better predictor of apoptosis (Std beta coefficient = 0.347, $P < 0.05$) than Caspase-3 proteins or mRNA; however, Caspase-3 at all levels correlated with apoptosis, inflammation and fibrosis (all $P < 0.01$). CONCLUSIONS: Up-regulation of apoptosis in remnant kidneys is likely to be Caspase-3-dependent as it is associated with increases in Caspase-3 at the activity, protein and mRNA levels. Therefore, Caspase-3 is a potential therapeutic target for the modification of renal cell apoptosis and subsequently renal fibrosis.